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On "Path Analysis in Genetic Epidemiology: A Critique"

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While the critique by Karlin et al. [1] was primarily concerned with recent applications of path analysis to genetic epidemiology by Rao and Morton [2, 3], Rice et al. [4], and Cloninger [5], it devoted much space to alleged shortcomings of path analysis in general. Since the latter authors are publishing a defense of their methods [6], I will confine myself largely to the defense of path analysis in general, a method that I proposed in 1918 [7], with first general account given in 1921 [8].

The purpose of this method is the evaluation of the relative importance of the various causes of variation in a particular population. It should be emphasized that it was concerned only with the precipitating variations due to causes, not with causes in an absolute sense. The development of characters in a population that has been made isogenic are absolutely dependent on an appropriate heredity and also on an appropriate environment. Both are absolutely necessary, and no evaluation of their relative importance is possible. Observed variation, however, must be due 100% to environmental variation, since none can be due to genetic variation by definition of "isogenic" (apart from very rare mutations).

Prof. W. E. Castle, my mentor as a graduate student, became involved in a controversy on whether differences in total size in a population are due predominantly to factors that affect the growth of all parts of the body alike or are merely due to the summation effect, on various parts separately. He asked his graduate students, H. D. Fish, and myself to calculate all of the 10 correlations among five bone measurements made by a former student in a rather heterogeneous population of rabbits. The 10 coefficients were all rather high (.558 to .758). Prof. Castle took this as supporting his position [9] in opposition to the view of certain others that racial crossing was likely to lead to disharmonious development in later generations.

The correlations were, however, far from perfect. It seemed of interest to attempt to make a more precise evaluation of the relative contributions of factors affecting general size, of ones affecting certain groups of measurements, and of ones with effects restricted to the particular measurement: to its squared standard deviations. The method arrived at was what was later called path analysis, except that the coefficients were the squares of the path coefficients.

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In a later paper [10] evaluating the relative importance of genetic and nongenetic factors on the percentage of white in the piebald patterns of a large random-bred stock of guinea pigs in comparison with that in a stock tracing to a single mating in the seventh generation of brother-sister mating (nearly zero percentage due to genetic variation), the term path coefficient was first used to avoid the ambiguity of the signs of the square roots of the previous coefficients of determination.

In both of these studies, the causal variables were unmeasured hypothetical ones, all broad classes. Path analysis is especially adapted to evaluating such broad classes, but in later cases, it was applied to mixtures of measurable and unmeasurable variable causes. The measurable ones had to be standardized for comparability, but this was necessary in any case for comparison on a uniform basis.

A specific factor such as an allele at a particular locus may increase general size, but does so disproportionately and thus contributes to more than one of the broad classes evaluated in the 1918 paper.

Karlin et al. give the following version of the general formula for path analysis: $\mathbf{y} = \Gamma\mathbf{x} + \mathbf{u}$, "where the components of **y** are measurable endogenous variables and those of **x** are exogenous variables that may or may not be measurable or even well defined. The matrix Γ contains the parameters of the model (path coefficients, loadings) and **u** includes error terms that are uncorrelated with each other and with **x**." They state that the above equation generates the covariance equation $C_y = \Gamma C_x \Gamma' + E$, "where C_y is the covariance matrix of the **y** variables, C_x that of the **x** variables, and E that of the residual variables **u**."

These expressions suggest a stereotyped approach, incompatible with the free choice of a causal pattern on the basis of all available evidence on which path analysis is based. In any case, this formulation seems to have little relation to the simple formula actually used to derive the set of simultaneous equations that are to be solved to obtain the path coefficients. Each equation is an analysis of a correlation coefficient.

This formula is merely that for the correlation between a variable, y, and another, x, that is represented as a linear function of certain causal variables, i, with determination of y made complete by including a residual, independent of the specified causes, $r_{xy} = \Sigma p_{xi}\, r_{iy}$, if y is represented as determined by causal variables, j. Application of the basic formula to itself gives $r_{xy} = \Sigma p_{xi} r_{ij}\, p_{yj}$.

The equations of the type r_{xy} may conveniently be read off from a "path diagram" in which each cause is related to its effect by an arrow (associated with a path coefficient p_{xi}, etc.), while unresolved correlations like r_{ij} above, between causes, are connected by a two-headed arrow, associated with the correlation.

Some of the immediate causes of x and y may be treated as effects of more remote causes and so on back, until ones treated as ultimate are reached. All of these, including the residuals, are to be connected by two-headed arrows as possibly correlated, unless there is reason to the contrary.

The correlation between any two variables in the system is the sum of contributions from all of the paths by which one may trace backward along arrows either to a common factor or to the middle of a two-headed one and then forward along arrows to the other specified variable. No variable may be passed through

more than once in the same compound path. Care must be taken that a variable that enters in two capacities, effect and cause, is exactly the same in both. One must never trace forward along an arrow and then backward on another since contributions to the same effect by two causes do not imply any correlation between them. Thus, there can never be more than one two-headed arrow in the same compound path.

In the case of reciprocal interactions [11] between variables x and y, equations $r_{xy} = \Sigma p_{xi} r_{iy}$ and $r_{xy} = \Sigma p_{yj} r_{jx}$ must be expanded separately. They provide independent equations.

In cases in which an adventitious correlation is imposed on two variables already represented as completely determined, correlations are imposed on the causes of the two, deducible by reversing the direction of the arrows pertaining to the causes. Cases arise in genetic epidemiology in which assortative mating imposes correlations between mates already represented as completely determined by heredity and environment. I carried out this procedure in an early paper [12] without using any symbols other than single and two-headed arrows. Cloninger [5] made the clarifying suggestion that such adventitious correlations be represented in the original path diagram by a headless bar with the injunction to reverse the directions of the arrows along the paths leading to the two variables in question.

While Karlin et al. do not give the usual basic formula, they give an illustration of the "rule" for calculating contributions to a given correlation. They give the correlation between certain variables x,y in a diagram quoted from Rao and Morton [3] as of the form $r_{xy} = r_1 r_2 + r_3 r_4 r_5 r_6 + r_7 r_8 r_9 r_{10}$ (not the subscript symbols used by them).

This violates the rule that a contribution to a correlation may include no more than one r (associated with a two-headed arrow). In the present case, the variables along all three of the connecting paths are connected only by single arrows so that the correlations between them are all equal to the corresponding path coefficient. The formula given by the usual rule $r_{xy} = p_1 p_2 + p_3 p_4 p_5 p_6 + p_7 p_8 p_9 p_{10}$ may be converted into the form given by Karlin et al. without numerical error. It must be reconverted into forms given by the rule as one of the simultaneous equations to be solved to obtain the values of parameters, here all p's. The conversion of all of the p's into r's is then misleading as an illustration of the rule and is a superfluous diversion in the solution.

It was recognized at the time of the first general account [8] that the method was essentially identical mathematically with Pearson's method of linear multiple regression [13] in estimating the value of one variable from known values of ones that are strongly correlated with it, while only weakly correlated with each other, so as to yield the maximum coefficient of multiple correlation with the given number of estimators. The pattern is stereotyped, with variables treated as linear functions of others. The solutions from standardized estimators must as a last step be multiplied by the ratio of the standard deviation of the variable estimated to that of the estimator in the term in question. The method is thus stereotyped and concrete in contrast with the unstereotyped, standardized method of causal path analysis. If concrete terms are used throughout, the method is the same as that proposed a century earlier by Gauss in his method of least squares as applied

to linear expressions, except that there is a difference in weighting that need not be discussed here.

The basic formula also applies to a different stereotyped pattern with standardized variables, that is, Spearman's factor analysis [14]. He seems to have had much the same idea I had several years later: to evaluate causal patterns in the determination of components of IQ in terms of general intelligence and special aspects. Factor analysts used stereotyped patterns in order to achieve complete objectivity. Their results can best be interpreted as giving a geometric representation of the variables as points in the "surface" of a multidimensional sphere, thereby revealing whatever clustering there is and suggesting common causes. The factors are (usually) orthogonal axes, and the factor loadings (path coefficients) are the coordinates of these. The method is applied to a set of variables that is treated as coordinate. Each of these is represented as determined by a set of hypothetical variables, yielding an array of similar simultaneous quadratic equations to be solved. Hotelling [15] devised an iterative method for finding the factor loadings with respect to the first axis, that accounts for the variables as far as possible in the sense of the method of least squares. The residuals were treated similarly with respect to a second axis and so on until all variance was exhausted. He showed that the number of axes must be the same as the number of measured variables including the self-correlations ($r_{xx} = 1$) as he did. Other factor analysts usually exclude the self-correlations until, as a final step, they are used to calculate a special axis for each measured variable. The number of axes other than special, required to practically exhaust variance, is usually much reduced, making it possible to grasp the clustering of variables much more easily than when there are many.

Tukey [16], in a critique of path analysis, expressed his conclusions as follows: "the briefest possible summing up of the writer's views is: 'very good but they don't go far enough.' In detail this view calls for regression in place of correlation." Turner and Stevens [17] also called for this substitution, and this is true of a number of social scientists [18, 19].

The use of concrete causal variables in an unstereotyped pattern does not, of course, lead to an evaluation of relative importance on a universal scale. The purpose is instead estimation.

It has been held that estimation based on causes instead of merely correlated estimators would be more stable under changes of conditions than with the latter. There may be some truth in this but the restriction of the causal variables to ones that are measured makes for a less acceptable causal pattern, and the restriction of estimators to ones that are causal tends to base estimation on weaker coefficients of multiple correlations. The usual consequences of causal multiple regression is inferior estimation.

The most important application of path analysis has probably been to a problem wholly different from those considered so far. This is to the effects of systems of mating [20]. If it is the path coefficients that are known, the basic formula can be used directly to calculate the correlation r_{xy} between the variables that are determined. Under diploid Mendelian heredity, it can be shown that the path coefficient for the relation between an arbitrary value assigned a gamete and the

zygote that results from the union with another gamete is: $a = \sqrt{1/[2(1 + F)]}$, where F is the correlation between the uniting gametes. The path relating one of these gametes to the zygote that has produced it is: $b = \sqrt{(1/2)(1 + F')}$, where the prime indicates the preceding generation. Thus the coefficient for the compound path, gamete to gamete, is $b\,a' = 1/2$, irrespective of inbreeding or gene frequencies. The compound path zygote to zygote is $a\,b = \sqrt{(1 + F')/(1 + F)}$, reducing to 1/2 at equilibrium where $F = F'$. It was possible by path analysis to extend the knowledge of the effects of inbreeding from self-fertilization and parent-offspring and brother-sister mating to any pattern of mating, regular or irregular. The general formula is $F = \Sigma[(1/2)^n(1 + F_A)]$, where F is the inbreeding coefficient (correlation) between uniting gametes, n is the number of gamete to gamete paths in a compound path through a common ancestor with inbreeding coefficient, F_A, and summation applies to all paths connecting the uniting gametes [21].

These correlations make possible a theoretical study of breeding structures of populations. A correlation is always a function of the population from which the gametes are drawn. The correlation relative to a subpopulation S, F_{IS}, rises toward F_{IT}, that relative to the total, T. The correlation between gametes drawn at random from a subpopulation, F_{ST}, falls off as the latter approaches the total, not taking account of effects of recurrent mutation or long-range dispersion which bring these processes to an end before the total is reached. These statistics are related by the equation $(1 - F_{IT}) = (1 - F_{IS})\,(1 - F_{ST})$. The theory has been extended to polysomic hetedity [22] and sex linkage [23].

Karlin et al. present various reasons for rejecting path analysis as a valid procedure. First, they consider that deviations from additivity and linearity in the effects of variable causes, and deviations from normality in the distributions, are so frequent that the method is practically useless. These objections apply just as much to linear multiple regression and factor analysis as to causal factor analysis. It is doubtful whether many statisticians are ready to abandon these methods, especially the former. Estimation from a set of linear normal equations, whether by Gauss's method of least squares or Pearson's multiple regression, is generally considered the most widely useful method that is available for this purpose. Factor analysis is at least widely considered a useful method for suggesting common causes.

It seems to be the usual experience that additivity and linearity in the relation of variables are approximated to an enormously greater extent than implied in the discussion of Karlin et al.

Variables that are products of others ($P = xy$) are indeed encountered very frequently and seem at first sight very far from additive and linear. We are concerned, however, only with deviations from the means:

$$\Delta P = P - \bar{P}, \qquad \Delta x = x - \bar{x}, \qquad \Delta y = y - \bar{y}_1$$

$$\bar{P} + \Delta P = (\bar{x} + \Delta x)(\bar{y} + \Delta y)$$

$$\Delta P = (\bar{x}\bar{y} - \bar{P}) + \bar{y}\Delta x + \bar{x}\Delta y + \Delta x \Delta y\ .$$

This is linear in Δx and Δy except for the quadratic term $\Delta x \Delta y$. This may be negligible if the coefficients of variation, $\Delta x/\sigma_x$, $\Delta y/\sigma_y$, are as small as they usually are for quantitative variation of organisms. If not negligible, it may be possible to estimate the average contribution to the variances of $\Delta x \Delta y$ as residual variances.

Where deviations from additivity are too great to be ignored, this may often be remedied by a transformation of scale, applied to all of the measurements before any calculations are made. This was done in the first paper in which the term path coefficient was used [10] and which was concerned with the roles of heredity and environment in determining the percentage of white in the coats of guinea pigs of two strains: random bred and closely inbred. Among 17 closely inbred strains, there was extreme positive skewness in the frequency distribution of all with small average percentages (but no wholly self-colored individuals) and extreme negative skewness, where the average percentages were high (but only a few individuals were black-eyed white). The probability integrals of the percentages of the individuals was used, essentially the same as the probit transformation proposed later [24]. This overcame the obvious damping of effects where percentages were close to 0 or 100 and normalized the frequency distributions.

Path analysis indicated that 42% of the total variance (.0.643) of the random-bred strain was genetic (genetic variance, .271), leaving .372 as its nongenetic variance. The total variance of the inbred strain (derived from a single mating in the seventh generation of brother-sister mating) was .364, in excellent agreement since the genetic component did not differ significantly from zero. In a later study [25], these same strains, but wholly different animals (the inbreds now being descended from a single mating in the 22nd generation of brother-sister mating), the total variance of the random-breds was .573, of which .233 was genetic (apart from a small sex difference) and .340 residual, which happened to agree exactly with the variances of the inbred strain. In other cases, a logarithmic transformation is indicated but the deviation from additivity and linearity is often so small that transformation is unnecessary.

Guinea pigs, like other species of the family *Caviidae*, normally lack thumb, big toe, and little toe, but little toes, ranging from vestigial to well developed, occur in many strains. This depends on multiple factors, genetic and environmental [27]. Assume an underlying normal distribution of factors with two thresholds, that for any development and that for perfect development. Assuming that the observed frequencies of three-toed, poor four-toed, and good four-toed constitute a trichotomy of a normal distribution, the standard deviations can be calculated in terms of an assumed unit distance between thresholds [27, 28]. Path analysis yields consistent results on the basis of this transformation [27, 28].

The sort of case in which deviations from additivity and linearity interfere seriously with path analysis can be illustrated by a study of the factors affecting the gains in weight of guinea pigs between birth and weaning at age 33 days. Size of litter (determined at conception as shown by its agreement with number of corpora lutea) has an obvious strong inverse effect, partly mitigated by stillbirths and postnatal deaths before weaning. Unfortunately, the relation between litter size and mortality of both sorts is highly nonlinear, the optimum size of litter

being three in a vigorous stock. It seemed best to omit mortality from the causal pattern, allowing its effect to be absorbed into that of size of litter.

The basic formula of path analysis is a property of the product-moment correlation coefficient. Its validity is destroyed if subjected to Fisher's z-transformation [29] before deriving an equation from it.

As noted earlier, the coefficient for a compound path, gamete to gamete a generation later, is exactly 1/2 irrespective of gene frequency. With frequencies .90A:.10a, the frequency distribution of zygotes under random mating is .81 *AA*: .18 A*a*:.01*aa*. An attempt to normalize this extremely skewed distribution would destroy the simplicity of the path coefficients and thus should not be made in analysis involving parent and offspring or other relatives. Transformation of the scale of measurement to improve additivity, made prior to any calculations, tends to give an approach to normality, but persistent skewness due to asymmetric gene frequencies should not be corrected.

The primary purpose of causal path analysis, the evaluation of the relative importance of the varying causes in a specified population, does not require a high degree of precision. Two significant figures are no doubt desirable, but one may be fairly satisfactory.

The conclusion seems warranted that with a scale of measurement designed to give approximate additivity, the usefulness of path analysis is restricted only rather infrequently by extreme nonlinearity of relations and that deviations from normality not corrected by transformation of scale should be ignored.

The second class of objections to path analysis raised by Karlin et al. had to do with the difficulties of solving a set of simultaneous equations that are not all linear, of choosing among multiple solutions, and of assigning confidence limits to any solutions that are obtained.

There is no serious difficulty except from possible large numbers if the equations are all linear as with linear multiple regression and some causal path analyses. Solution may be facilitated by use of Gauss's algorithm.

In the case of factor analysis, a set of coordinate measured variables are represented as determined by a set of hypothetical ones. The equations to be solved are all similar quadratics. There are an infinite number of solutions corresponding to rotations of the set of vectors representing the variables. Hotelling's iterative method [15] was a least-square method of finding the factor loadings (path coefficients) of orthogonal axes corresponding to the factors that maximize the variables attributable to a first general factor. Application to the residuals maximizes the amount attributable to the second factor and so on until all the variances are exhausted. If the self-correlations are included in the correlation matrix, the number of factors equals the number of measured variables according to Hotelling. There is necessarily a balancing of plus and minus values of the factor loadings beyond those of the first set.

As noted earlier, most factor analysts prefer to omit the self-correlations until they are used in a final step of finding special factor loadings for each observed variable.

For a causal path analysis of a set of coordinate measured variables in terms of general, group, and special factors, the contamination of the first factor by contributions from group factors, the set of correlations to be used in deriving a

set of simultaneous equations should be restricted to those which on trial yield no significant residuals. The same procedure should be used in calculating the path coefficients pertaining to successive group factors.

In studies [30, 36] of seven measurements (weight, length, and breadth) of skull, ear length, lengths of humerus, femur, and tibia of 27 F_1 rabbits from a cross between the Flemish Giant breed and the Polish Dwarf breed, the former 3.4 times as heavy on the average as the latter, 18 of the 21 correlation coefficients yielded path coefficients for a maximized first factor with no significant residuals. The same was true for those same measurements of the enormously more variable set of 112 F_2 rabbits. In both cases, the only three correlations with significant residuals were those among the leg bones, that between femur and tibia being much the greatest. A general factor, a leg factor, and a hind leg factor were all that were indicated in both cases apart from the seven special factors.

Somewhat similarly, path analysis of six bone measurements of 276 hens from a flock of White Leghorns [30, 35] yielded an important factor for general size from 12 of the 15 correlations with no significant residuals. The three exceptions yielded group factors for two skull measurements for lengths of humerus and ulna and for lengths of femur and tibia in addition to the six special factors. In contrast with the rabbits, there was no factor for the limbs collectively.

In path analyses of coordinate variables, in which no general factor was expected, none was found. There were merely group and special factors.

In some path analyses, the number of simultaneous equations derivable from known correlations fell short of the number of unknown parameters. Only conditional solutions were possible, if simplification of the causal pattern seemed too unrealistic.

Burks [31] obtained IQs for 214 children, aged 5–14, adopted at average age 3 months, the mental ages of their parents and indices of the home environments from a California population, white and non-Jewish. She did the same with a carefully selected control group of 105 children reared by their own parents.

The correlations among the variables in the two sets were very different, clearly indicating an important influence of heredity in the control data. Burks attempted to make an evaluation by path analysis but confused this with multiple regression. I published a note [32] giving what I considered a more adequate analysis. The number of unknown parameters in the simplest pattern that seemed at all adequate was greater than the number of independent equations for their solutions, permitting only a range of possible evaluations, heritability less than 80% but greater than 50%. About 30% of the variance could not be apportioned among unmeasured environment, heredity, and interaction between them.

I reconsidered the problem many years later [33] using what I then considered a more adequate causal pattern, but the final evaluation differed little: a possible range from 45% to 80% heritability.

In this case, I also reviewed data from monozygotic and dizygotic twins as well as from ordinary siblings. These present, in principle, a means of separating out nonadditive heredity, but unfortunately require controversial assumptions with respect to possible environmental differences. Studies of monozygotic twins reared apart were plagued by evidence that the most numerous data of this sort

were fraudulent. Omitting those, analysis indicates heritability closer to the upper than to the lower limit (in white populations), but data of other sorts that have been suggested are needed. Where the number of equations was slightly in excess of the unknown parameters, there was room for possible elaboration of the causal pattern.

In cases in which the number of equations was markedly in excess and some or all were nonlinear, solution by such methods as that of least squares or maximum likelihood may seem impracticable. In a study of deviations from trend of various corn and hog variables in the period between the Civil War and World War I [34], 374 correlation coefficients were calculated. In other cases in which interacting variables were considered over a period of time, the numbers of correlations were fairly large. In such cases, attention has been paid primarily to the large correlations over short intervals of time. Preliminary estimates might be made from simplified causal patterns as a basis for solutions by trial and error of the full causal pattern during the intervals. The usually smaller correlations and more complicated equations relating to larger intervals of time could be used as checks.

In the case of the hog and corn variables, a central system that included the larger correlations was analyzed first. This consisted of the price of corn (as an independent variable), the prices of the homogenous winter hog pack (November to February) at Western markets, the prices of the highly heterogenous summer pack (March to October), and a hypothetical variable: the amount of breeding for which the contemporary live weight and the winter pack a year and a half later were indices. (Correlation between them was +.78.) After finding 13 path coefficients to the nearest .05 by trial and error, a second system for each season's pack, live weight, and pork (the product) was appended to the central system, and 16 path coefficients were found by trial and error, again to the nearest .05. Including three coefficients relating corn acreage, yield, and crop (the product), and price, 32 path coefficients accounted for all of the 374 correlations as closely as the numbers warranted. The corn variables, dependent primarily on yield and hence weather, set going a rapidly damped 4-year cycle of deviations in the hog variables. Such methods are no doubt far from ideal from the mathematical standpoint but it is believed contributed to understanding of what was going on in the populations studied.

Testing was also far from ideal from the mathematical standpoint. The situations in which standard errors could be deduced were discussed [35] but these do not go far. The standard errors of the observed correlation coefficients provide a rough indication of the levels of precision among the path coefficients deduced from them. The best indication is provided by the degree of consistency of the results from analyses of similar populations, perhaps subdivisions of the total set.

Toward the end of their paper, Karlin et al. go into three alternative ways of dealing with complex structural data. "(1) One can assume the validity of a specific modeling form (e.g., linear additive models such as those used in path analysis and variance component analysis) and try to improve estimation and hypothesis testing within that framework. It is this approach that we have criticized in this paper.

"(2) One can successively examine different classes of models while remaining committed to the modeling approach itself.

"(3) Finally, and we think most fruitfully, one can adopt an essentially model-free approach, seeking to understand the data interactively by using a battery of displays, indices, and contrasts. This approach emphasizes the concept of robustness in interpreting results."

The first alternative refers to isolated path analyses. The second corresponds to the usual treatment of path analysis as an exploratory procedure with frequent comparisons of the results in different populations that differ more or less in conditions and with frequent comparisons of the effects of different assumptions with respect to the causal system [36]. The unstereotyped approach of path analysis differs profoundly from the stereotyped modes of description designed to avoid any departures from complete objectivity. The latter has its proper place in which path analysis is not intended as an alternative, but exploratory investigation of path analysis also has a place in increasing understanding of what is actually going on in a population that has been described as objectively as possible.

The obvious distrust of Karlin et al. for the unavoidably somewhat subjective investigation of causes is reminiscent of the first published criticism of path analysis: that by Niles [37], replied to by Wright [38], but does not go as far. Niles disapproved of any use of the concept of causation, urging its replacement by correlation. He urged the use of headless bars in place of arrows in path diagrams. He objected to the use of different structural patterns in different cases, preferring a stereotyped approach to an unstereotyped one. In treating the model-free approach (3) as preferred alternative to (1) and (2), Karlin et al. are urging not merely a change in method, but an abandonment of the purpose of path analysis and evaluation of the relative importance of varying causes. There can be no such evaluation without a model. Their advice to anyone with an urge to make such an evaluation is to repress it and do something else.

Summing up, the paper by Karlin et al. is rich in precautions that should be borne in mind in any analysis of causal systems but I find no reason to modify my conviction that proper utilization of path analysis as an exploratory procedure can add greatly to our understanding of what is happening in systems of correlated variables including ones concerned with human genetic epidemiology.

REFERENCES

1. KARLIN S, CAMERON EC, CHAKRABORTY R: Path analysis in genetic epidemiology: a critique. *Am J Hum Genet* 35:695–732, 1983
2. RAO DC, MORTON NE: IQ as a paradigm in genetic epidemiology, in *Genetic Epidemiology*, edited by MORTON NE, CHUNG CS, New York, Academic Press, 1978, pp 145–195
3. RAO DC, MORTON NE: Path analysis of quantitative inheritance, in *Current Developments in Anthropological Genetics*, edited by MIELKE JH, CRAWFORD MH, New York, Plenum Press, 1980, pp 355–372
4. RICE J, CLONINGER CR, REICH T: Analysis of behavioral traits in the presence of cultural transmission and assortative mating: application to IQ and SES. *Behav Genet* 10:73–92, 1980
5. CLONINGER CR: Interpretations of intrinsic and extrinsic structural relations by path analysis: theory and applications to assortative mating. *Genet Res* 36:133–146, 1980

6. CLONINGER CR, RAO DC, RICE J, REICH T, MORTON NE: A defense of path analysis in genetic epidemiology. *Am J Hum Genet* 35:733–756, 1983
7. WRIGHT S: On the nature of size factors. *Genetics* 3:367–374, 1918
8. WRIGHT S: Correlation and causation. *J Agric Res* 20:557–585, 1921
9. CASTLE WE: The nature of size factors as indicated by correlation. Washington, D.C., Carnegie Institute, no. 196:51–55, 1914
10. WRIGHT S: The relative importance of heredity and environment in determining the piebald pattern of guinea pigs. *Proc Natl Acad Sci USA* 6:320–332, 1920
11. WRIGHT S: The treatment of reciprocal interactions, with or without lag, by path analysis. *Biometrics* 16:423–445, 1960
12. WRIGHT S: Systems of mating III. Assortative mating based on somatic resemblance. *Genetics* 6:144–161, 1921
13. PEARSON K: Mathematical contributions to the theory of evolution in regression, heredity and panmixis. *Philos Trans R Soc Lond [Biol]* 187:253–318, 1896
14. SPEARMAN C: General intelligence objectively determined and measured. *Am J Psychiatry* 15:201–222, 1904
15. HOTELLING H: Simplified calculations of principle components. *Psychometrics* 1:27–35, 1936
16. TUKEY JW: Causation, regression and path analysis, in *Statistics and Mathematics in Biology*, edited by KEMPHORN O, BANCROFT TA, GOWEN JW, LUSH JL, Ames, Iowa State Univ. Press, 1954, pp 35–66
17. TURNER ME, STEVENS CD: The regression analysis of causal paths. *Biometrics* 15:236–258, 1959
18. GOLDBERGER AS, DUNCAN OD: *Structural Equation Models in the Social Sciences*. New York and London, Seminar Press, 1973
19. DUNCAN OD: *Introduction to Structural Equation Models*. New York, San Francisco, and London, Academic Press, 1975
20. WRIGHT S: Systems of mating: II. The effects of inbreeding on the genetic composition of a population. *Genetics* 6:124–143, 1921
21. WRIGHT S: Mendelian analysis of the pure breeds of livestock. I. The measurement of inbreeding and relationship. *J Hered* 14:339–348, 1923
22. WRIGHT S: The distribution of gene frequencies in populations of polyploids. *Proc Natl Acad Sci USA* 24:372–377, 1938
23. WRIGHT S: Inbreeding and homozygosis. *Proc Natl Acad Sci USA* 19:411–420, 1933
24. BLISS CJ: The calculation of the dosage mortality curve. *Ann Appl Biol* 22:134–167, 1935
25. WRIGHT S, CHASE HD: On the genetics of the spotted pattern of the guinea pig. *Genetics* 21:758–787, 1936
26. WRIGHT S: *Evolution and the Genetics of Populations*, vol 3, *Experimental Results and Evolutionary Deductions*. Chicago, Univ. of Chicago Press, 1977, chap. 4
27. WRIGHT S: The results of crosses between inbred strains of guinea pigs, differing in number of digits. *Genetics* 19:537–551, 1934
28. WRIGHT S: Analysis of variability in number of digits in an inbred strain of guinea pigs. *Genetics* 19:506–536, 1934
29. FISHER RA: On the probable error of a coefficient of correlation deduced from a small sample. *Metron* 4:1–32, 1921
30. WRIGHT S: General, group and special size factors. *Genetics* 17:603–619, 1932
31. BURKS BS: The relative influence of nature and nuture upon mental development and true parent true children resemblance, in *The 27th Yearbook of the National Society for the Study of Education*, Bloomington, Ill., Public School Publishing, 1928, pp
32. 219–316
WRIGHT S: Statistical methods in biology. *J Am Stat Assoc* 26(Suppl.):155–163, 1931
33. WRIGHT S: *Evolution and the Genetics of Populations*, vol 4, *Variability within and among Natural Populations*. Chicago, Univ. of Chicago Press, 1978

34. WRIGHT S: Corn and hog correlations. Washington, D.C., U.S. Dept. of Agriculture, bulletin no. 1300, 1925
35. WRIGHT S: The method of path coefficients. *Ann Math Stat* 5:161–215, 1934
36. WRIGHT S: *Evolution and the Genetics of Populations*, vol 1, *Genetic and Biometric Foundations*. Chicago, Univ. of Chicago Press, 1968
37. NILES HE: Correlation causation and Wright's theory of path coefficients. *Genetics* 7:258–273, 1922
38. WRIGHT S: The theory of path coefficients: a reply to Niles' criticism. *Genetics* 8:239–255, 1923